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Variance and Dissent

RELATIONSHIP OF THYROID DISEASE AND USE OF THYROID SUPPLEMENTS TO BREAST CANCER RISK

LOUISE A. BRINTON, DANIEL A. HOFFMAN, ROBERT HOOVER and JOSEPH F. FRAUMENI JR

Environmental Epidemiology Branch, National Cancer Institute, Landow Building, Room 3C06, Bethesda, MD 20205, U.S.A.

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Abstract—An interview study of 1362 breast cancer cases and 1250 controls identified through a multi-center screening program allowed evaluation of effects of thyroid disease and supplementation on breast cancer risk. A previous diagnosis of treated thyroid disease was not associated with an excess risk (RR = 1.0), nor were any specific diagnoses, including hypothyroidism, hyperthyroidism, or goiter. Although based on limited numbers, women with untreated hypothyroidism or goiter had a significantly reduced risk of breast cancer (RR = 0.3, 95% CI 0.1–0.7). Thyroid supplementation for non-disease reasons (primarily weight loss and fertility problems) was associated with a slight elevation in breast cancer risk (RR = 1.2, 95% CI 0.9–1.7), but patterns of risk by duration and latency generally failed to provide evidence of causality. Elevated risks were noted among women who received thyroid medications for fertility problems (RR = 4.2) and among those with a family history of breast cancer (RR = 2.6) or a late age at first childbirth (RR = 2.4), possibly indicating an hormonal interaction.

INTRODUCTION

THE RELATIONSHIP between thyroid disease and breast cancer has been of interest ever since Beatson [1] reported a beneficial effect of thyroid extract among patients with metastatic breast cancer. Although animal studies have provided evidence for an effect of endogenous thyroid function on mammary development [2, 3], epidemiologic studies on the role of thyroid dysfunction and breast cancer etiology have produced conflicting results. Some studies have shown an increased breast cancer risk among patients with hypothyroidism [4], autoimmune thyroiditis [5] and hyperthyroidism [6], while others have demonstrated a decreased risk associated with either hypothyroidism [7] or hyperthyroidism [8]. Several studies [9–14] have failed to find any relationship between thyroid disease and breast cancer.

Further controversy has arisen regarding the possible role of thyroid replacement therapy in the etiology of breast cancer. Kapdi and Wolfe [15] reported an increased risk associated with thyroid supplementation, particularly among nulliparous women treated for more than 15 years. However, the design and interpretation of this study have been criticized [16], and subsequent studies [17–19] failed to confirm an association between thyroid medications and risk of breast cancer.

In an effort to clarify these relationships, we analyzed information regarding the diagnosis of thyroid disease, use of thyroid supplements and reasons for prescription among a large series of breast cancer cases and normal subjects identified through a multi-center breast cancer screening program. A substantial proportion of women in this study received thyroid supplements for reasons other than thyroid disease, allowing the effects of thyroid supplementation to be distinguished from those of thyroid disease.

METHODS

Study subjects consisted of participants in the Breast Cancer Detection Demonstration Project (BCDDP), a multi-center breast cancer screening program involving over 280,000

women at 29 widely dispersed centers. This program, jointly sponsored by the American Cancer Society and the National Cancer Institute, recruited women between 1973 and 1975 for a five-year program of annual breast examinations by the combined modalities of clinical examination, mammography and thermography. The present investigation used a case–control approach, including as cases women at 28 centers whose breast cancer was detected during the period July 1973 through May 1977. Control subjects were selected from women who had not received a recommendation for biopsy during the course of screening participation. The controls were chosen to be comparable to the cases on center, race (white, black, Oriental, other), age (same 5-year group). time of entry (same 6-month group) and length of continuation in the program (controls had to have at least as many years of screening as cases).

Exposure information was obtained during home interviews that averaged approximately 40 min and were conducted by trained nurse interviewers. Completed interviews were obtained from 1552 cases (86.1% of eligible subjects) and 1375 controls (74.2%). The lower response rate for controls than for cases was primarily due to controls having moved and being unavailable for interview (12.9% of controls vs 5.0% of cases) and to their refusing to be interviewed (10.5% vs 4.6%). In addition, 2.4% of the controls and 4.3% of the cases were deceased. Women who were interviewed, however, were not found to differ significantly from those not interviewed with regard to a number of factors determined for each women at the time of entry to the screening project, including age, race, family income and history of breast surgery.

The cases were interviewed at various intervals after diagnosis. However, in the analyses, exposure information was truncated at the time of diagnosis for cases or an equivalent time for controls. Women who reported a history of breast cancer prior to entering the Project (60 cases, 11 controls) were excluded from analysis. Analyses were also restricted to white subjects (91% of the entire study population). The final study groups consisted of 1362 cases and 1250 controls.

The measure of association used for evaluating effects of exposure factors is the relative risk (RR), as estimated by the odds ratio. Confounding variables were evaluated by stratified techniques, deriving maximum likelihood estimates of combined ratios and 95% confidence intervals (CI) [20]. For multiple levels of exposure, significance was assessed using a one-tailed linear trend test [21].

RESULTS

A total of 28.2% of the cases and 29.2% of the controls reported a history of physician diagnosed thyroid disease, resulting in a RR of 1.0 (95% CI 0.8–1.1). This estimate was not appreciably altered by adjustment for a variety of breast cancer risk factors, including family history of breast cancer, parity, age at first childbirth, history of surgery for benign breast disease, age at menarche, type of menopause, obesity, years of education, or income. In addition, little variation in risk estimates were seen across categories of age at breast cancer diagnosis and menopausal status of the study subjects.

Further analysis considered the type of thyroid disease and whether or not treatment had been prescribed (Table 1). This revealed similar risks for the separate diagnoses of hypothyroidism (1.0), goiter (0.9), and hyperthyroidism (1.0), but differing risks according to history of medication usage. No alterations in risk were noted for any of the conditions for

TABLE 1. RELATIVE RISKS OF BREAST CANCER BY PREVIOUS DIAGNOSIS AND THERAPY FOR THYROID DISEASE

Type of thyroid disease	No medication			Medication prescribed			Total		
	Cases	Controls	RR (95% CI)	Cases	Controls	RR (95% CI)	Cases	Controls	RR (95% CI)
Hypothyrodism	1	4	0.23 (0.0–1.7)	219	191	1.04 (0.8–1.3)	221	199	1.00 (0.8–1.2)
Goiter	6	16	0.34 (0.1–0.8)	27	19	1.29 (0.7–2.3)	33	35	0.85 (0.5–1.6)
Hyperthyrodism	2	2	0.90 (0.1–6.4)	32	29	1.00 (0.6–1.7)	34	31	0.99 (0.6–1.7)
Unspecified	17	22	0.70 (0.4–1.3)	73	71	0.93 (0.7–1.3)	95	98	0.88 (0.6 1.2)

All risks relative to subjects without a history of thyroid disease (975 cases, 882 controls).
Analysis excludes 4 cases and 5 controls with unknown information on history of thyroid disease.
Six cases and 9 controls were also unable to provide information regarding whether medication was ever prescribed for thyroid disease.

which medication had been prescribed, with the risks being 1.0 for treated hypothyroidism or hyperthyroidism and 1.3 for goiter. There was, however, some evidence of a decrease in risk for women whose thyroid disease was not medically treated. Among those not taking thyroid medications, the relative risks were 0.2 for hypothyroidism, 0.9 for hyperthyroidism and 0.3 for goiter. This latter estimate was statistically significant, although the number of subjects involved was limited (6 cases, 16 controls).

Euthyroid women were asked about their use of thyroid medications for purposes other than thyroid disease (Table 2). A substantial proportion of these women (9.2% of cases, 7.4% of controls) reported taking thyroid medications for these reasons, resulting in a relative risk of 1.2 (95% CI 0.9–1.7). Approximately 50% of women in this category used thyroid medications for weight loss, with such usage associated with a RR of 1.4 (0.8–2.4). Other reasons for use included supplementation during pregnancy (RR = 1.1) and for regulation of menstrual periods (1.2). Nine cases and two controls reported use for fertility problems, an exposure associated with a non-significant 4-fold elevation in risk.

These findings were evaluated further after control for potential confounding variables. In particular, there was concern about the intervening effects of weight, height and Quetelet's index (a measure of obesity) on the risk associated with taking thyroid medications for weight loss and of reproductive factors (number of livebirths and age at first livebirth) on the risk associated with use for fertility reasons. While obesity [22] and nulliparity or late age at first childbirth [23] have been associated with an increased breast cancer risk, control for these factors did not substantially alter any of the crude estimates, nor did control for a variety of other risk factors, including family history of breast cancer, history of surgery for benign breast disease, age at menarche, type of menopause, years of education or income.

Further analyses considered various parameters of use of thyroid medications according to the reasons for use (Table 3). There was no significant trend overall according to age at first use of thyroid medications, years of use, years since initial use or years since last use. In women taking supplements for thyroid disease there was also no evidence of any trends according to various parameters of use. Among euthyroid women, although a significantly elevated risk (1.8) was associated with thyroid medication use that began prior to age 30, no significant trend of risk across age at first use was noted. In addition, no significant relationships were observed according to years of use or years since initial use. Euthyroid women taking thyroid hormones at the time of diagnosis were at the highest risk (4.7), although this finding was based on a small number of exposed women, and no other trends were observed according to years since last use.

The relationship between use of thyroid supplements among euthyroid women and risk of breast cancer was also examined according to the presence of other risk factors (Table 4). Elevated risks were associated with thyroid medication use in those with a family history of breast cancer (RR = 2.6, 95% CI 0.9–7.6) and those without a history of benign breast disease (1.5, 1.0–2.1). There was, however, no evidence that use of thyroid supplements altered risk according to varying levels of age at menarche, Quetelet's index, height, or

TABLE 2. RELATIVE RISKS OF BREAST CANCER AMONG EUTHYROID WOMEN BY USE OF THYROID MEDICATIONS FOR REASONS OTHER THAN THYROID DISEASE

	Cases	Controls	Relative risk	(95% CI)
Use of thyroid medications for other reasons				
No	884	811	1.00	—
Yes	90	66	1.23	(0.9–1.7)
Unknown	5	10	0.51	(0.2–1.5)
Reasons for use				
To lose weight	42	27	1.43	(0.8–2.4)
During pregnancy	5	4	1.14	(0.3–5.1)
For fertility problems	9	2	4.17	(0.8–28.1)
To regulate menses	10	8	1.16	(0.4–3.2)
Other reasons	22	16	1.19	(0.6–2.4)
Unknown	2	9	0.16	(0.1–0.6)

Women with thyroid disease are excluded.
Relative risks adjusted for age of breast cancer diagnosis of study subjects.

TABLE 3. RELATIVE RISKS OF BREAST CANCER BY SELECTED PARAMETERS OF THYROID MEDICATION USE AND REASONS FOR USE

	Thyroid disease	Other use	Total
Age at first use			
<30	1.00 (109)	1.79*(41)	1.14 (150)
30–39	0.90 (81)	0.64 (16)	0.84 (97)
40–49	1.08 (60)	1.73 (17)	1.18 (77)
50–59	1.00 (36)	0.61 (2)	0.97 (38)
60+	2.57 (14)	0.00 (0)	2.14 (14)
Unknown	1.23 (51)	1.28 (14)	1.24 (65)
Years of use			
<5	1.02 (157)	1.22 (68)	1.08 (225)
5–9	1.72* (47)	0.73 (4)	1.56 (51)
10–14	1.16 (38)	1.38 (3)	1.18 (41)
15+	0.82 (72)	0.92 (4)	0.82 (76)
Unknown	1.03 (37)	2.02 (11)	1.16 (48)
X_1 for trend	−0.26	0.51	−0.32
Years since initial use			
<10	1.18 (76)	0.73 (8)	1.12 (84)
10–19	0.92 (75)	1.05 (24)	0.95 (99)
20+	0.99 (149)	1.55 (44)	1.08 (193)
Unknown	1.23 (51)	1.28 (14)	1.24 (65)
X_1 for trend	−0.18	1.52	0.47
Years since last use			
Current user	1.09 (84)	4.59 (5)	1.13 (89)
1	0.84 (65)	0.31 (2)	0.80 (67)
2–9	1.22 (36)	0.73 (8)	1.09 (44)
10–19	1.07 (42)	1.30 (24)	1.14 (66)
20+	1.00 (73)	1.48 (37)	1.12 (110)
Unknown	1.23 (51)	1.28 (14)	1.24 (65)

Numbers of cases are shown in parentheses.
All risks relative to women without thyroid disease who reported no prior use of thyroid supplements (884 cases, 811 controls). Relative risks presented are unadjusted; age adjusted risks are virtually identical.
Trend statistics exclude unknowns.
*$p < 0.05$.

TABLE 4. RELATIVE RISKS OF BREAST CANCER ASSOCIATED WITH USE OF THYROID SUPPLEMENTS BY SELECTED BREAST CANCER RISK FACTORS

	Cases		Controls		
Selected risk factors	Total	Exposed	Total	Exposed	Relative risk (95% CI)
Family history of breast cancer					
No	747	67	776	61	1.16 (0.8–1.7)
Yes	223	22	100	4	2.63 (0.9–7.6)
History of benign breast surgery					
No	749	77	720	52	1.47 (1.0–2.1)
Yes	225	13	157	14	0.63 (0.3–1.4)
Quetelet's index					
<22	292	21	258	21	0.87 (0.5–1.6)
22–23	246	18	244	10	1.85 (0.8–4.0)
24–25	167	14	157	8	1.70 (0.7–4.1)
26+	269	37	215	27	1.11 (0.6–1.9)
Age at first livebirth					
<20	76	6	100	5	1.63 (0.5–5.5)
20–24	304	24	323	28	0.90 (0.5–1.6)
25–29	294	25	232	15	1.34 (0.7–2.6)
30+	136	18	83	5	2.38 (0.9–6.5)
Nulliparous	162	17	139	13	1.14 (0.5–2.4)
Age at menarche					
<12	169	19	136	12	1.31 (0.6–2.8)
12	235	22	197	17	1.09 (0.6–2.1)
13	285	25	265	17	1.40 (0.7–2.6)
14	153	12	130	7	1.50 (0.6–3.9)
15+	123	10	145	12	0.98 (0.4–2.4)

Relative risks represent ever use of thyroid supplements among euthyroid women vs no use within each risk factor category.
Family history category refers to those with a history of breast cancer in a first degree relative, i.e. mother, sister or daughter.
Quetelet's index, a measure of obesity, is calculated as: [weight (in kg) divided by height (in cm)] × 100.
Unknowns are excluded from analysis.

weight. No elevation in risk (RR = 1.0) was associated with thyroid use among nulliparous women, but those with later ages (30+) at first livebirth were adversely affected (RR = 2.4, 95% CI 0.9–6.5). This association was independent of the risk associated with using thyroid supplements in conjunction with fertility problems.

Associations were evaluated further according to years of use and years since initial use of thyroid supplements among euthyroid women within risk factor categories. There was no evidence of significant trends in risk according to years of use within any of the categories. Analysis of years since initial use, however, showed elevations in risk associated with extended intervals since first use (20+ years) among women with a family history of breast cancer (RR = 3.7), those with no previous breast biopsies (1.6) and those with a first livebirth after age 30 (1.8).

DISCUSSION

In this study, we found no evidence that a prior diagnosis of thyroid disease was associated with the risk of breast cancer, a finding consistent with a number of other case–control studies [17–19, 24–27]. Ascertainment of information on thyroid disease through patient recall may be subject to question, particularly since our rate of prior thyroid disease among control subjects (29%) was substantially higher than prevalence rates of 3–4% reported elsewhere [28], undoubtedly reflecting the greater health consciousness of women who volunteer for periodic breast screening. Despite the high reported rates of prior thyroid disease, we found no elevated risk of breast cancer for any of the categories of thyroid diseases considered, including hyperthyroidism, hypothyroidism, goiter or undefined types of thyroid disease. These results also agree with the majority of prospective studies that have determined rates of breast cancer among women with specific diagnoses of thyroid disease [11–14]. Discrepancies between these studies and those reporting an effect of thyroid disease on breast cancer risk [4, 6, 8] are likely to be due to methodologic limitations of many of the latter investigations, including small study populations and short observation periods. Some further attention may, however, be warranted for autoimmune thyroiditis, since a study in Japan [5] showed an increased risk of breast cancer among these patients, although this was not confirmed in a U.S. study [11].

In addition to assessing the relationship of thyroid disease to breast cancer risk, our study enabled an evaluation of the effects of thyroid supplementation. This is of special interest since Kapdi and Wolfe [15] reported elevated breast cancer risks among long-term users of thyroid preparations. Evaluation of this issue is complicated by the fact that thyroid medications are prescribed not only for thyroid disease, but also for a variety of other conditions, including obesity and fertility problems. Because our questionnaire elicited information on the reasons for prescription, we were able to evaluate effects separately according to the underlying conditions while accounting for the effects of several confounding variables.

No excess risk of breast cancer was seen among women receiving supplements for treatment of thyroid disease. However, we did find some evidence that women with untreated hypothyroidism or goiter were at a significantly decreased risk (0.3), whereas those who were treated showed no alteration in risk (1.1). This suggests that endogenous thyroid hormones may contribute to the baseline incidence patterns of breast cancer. However, other explanations for the low risk are possible; since untreated women comprised only a small proportion (6.2%) of those with hypothyroidism or goiter, the finding could reflect a chance event or an association with a particular type of thyroid disease not requiring treatment. Our results support the observation [7] that hypothyroidism confers a protective effect on breast cancer risk that is removed by thyroid supplementation, but are inconsistent with correlational studies linking high rates of breast cancer to endemic goiter areas [4, 29].

Of further interest in this study was the slight excess risk (RR = 1.2) of breast cancer among euthyroid women given supplements for other reasons. For the most part, the individual indications did not show significant elevations in risk, nor were there any significant trends in risk by duration of use, latency period or age at exposure. However, a

4-fold excess risk of breast cancer was observed among women who reported use for fertility problems, although this finding was based on small numbers (9 cases, 2 controls) and the reasons for the elevation are unclear. Rather than a direct effect of thyroid supplementation, the finding, if real, may reflect a high risk of breast cancer among women with hormonal causes of infertility. This issue has been investigated among infertile women with progesterone deficiencies [30], but it would be of interest to evaluate breast cancer risk among women whose infertility is associated with endogenous thyroid hormone abnormalities.

In addition to examining effects according to the indication for thyroid supplementation, we were also interested in determining whether associations varied according to the presence of other breast cancer risk factors. Although Kapdi and Wolfe [15] previously reported an adverse effect of long-term thyroid supplementation among nulliparous women, we found no excess risk associated with ever use or long-term use among this subgroup. However, we did find increased risks associated with use of thyroid medications among euthyroid women with a family history of breast cancer (RR = 2.6) and those with a first livebirth after age 30 (RR = 2.4). Although chance associations cannot be excluded, it may be that exogenous thyroid hormones contribute to the endogenous hormonal alterations associated with a family history of breast cancer [30] or a late age at first childbirth [31, 32].

The discrepancy between our results and those of the previous investigation showing an increased risk of breast cancer among users of thyroid supplements [15] may relate to effects of a possible selection bias in the latter study. Since cases in that study were often referral patients, while controls comprised asymptomatic volunteers in a screening program, the positive association may have reflected selective screening based on suspicious breast lumps and current use of thyroid supplements. Our study avoided this particular selection bias by selecting cases and controls from the same population of asymptomatic women presenting for routine screening. In addition, our study avoided criticisms aimed at previous negative case–control studies, since our controls were normal screenees rather than hospitalized patients who may be excessively exposed to thyroid supplements. Thus, the findings of this study of no substantial alteration in breast cancer risk associated with a previous diagnosis of thyroid disease or with use of thyroid supplements, either for treatment of thyroid disease or for other reasons, are generally reassuring. Somewhat difficult to interpret are the slight elevations in risk among several subgroups in this study, namely women receiving thyroid medications for fertility problems or in conjunction with a family history of breast cancer or a late age at first childbirth. Although based on limited numbers, and possibly reflecting chance associations or effects of selection bias, the relationships warrant further investigation.

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